



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 69/95, 67/40, 67/52	A1	(11) International Publication Number: WO 98/56750 (43) International Publication Date: 17 December 1998 (17.12.98)
<p>(21) International Application Number: PCT/EP98/03221</p> <p>(22) International Filing Date: 29 May 1998 (29.05.98)</p> <p>(30) Priority Data: MI97A001375 11 June 1997 (11.06.97) IT</p> <p>(71) Applicant (for all designated States except US): SYNTECO S.R.L. [IT/IT]; Via Parco del Ticino, 10, I-27028 S. Martino Siccomario (IT).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): SINISTRI, Monica [IT/IT]; Via Ugo Foscolo, 3, I-27100 Pavia (IT). SINISTRI, Roberta [IT/IT]; Via Ugo Foscolo, 3, I-27100 Pavia (IT).</p> <p>(74) Agent: MINOJA, Fabrizio; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: A PROCESS FOR THE PREPARATION OF DIACEREIN</p>		
<p>(57) Abstract</p> <p>A process for the preparation of diacerein characterized by purification of crude diacerein by salificating it with an organic acid alkali salt and subsequent conversion to the acid form with diluted acids.</p>		

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A PROCESS FOR THE PREPARATION OF DIACEREIN

The present invention relates to a process for the preparation of diacerein.

Diacerein or diacetylrein (1,8-diacetoxy-3-carboxyanthraquinone) is a known antiarthritic medicament used for some time in clinical practice.

Different processes for the preparation of diacerein are known: for example, FR-A-2508798 describes the acetylation of rein (1,8-dihydroxyanthraquinone-3-carboxylic acid), with an acetic anhydride excess in the presence of sulfuric acid.

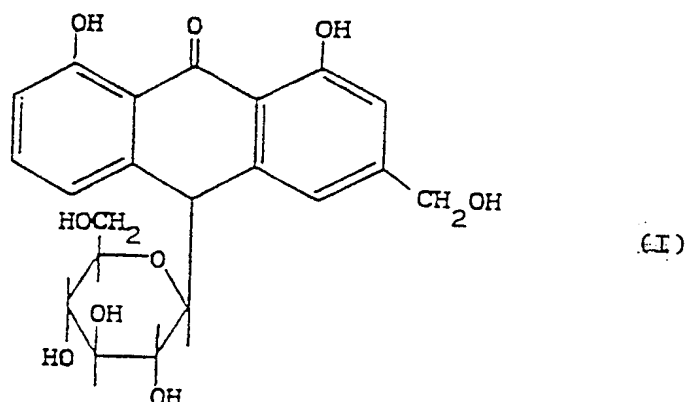
EP-A-636602 discloses a preparation process characterized by purificating the crude diacerein by crystallization from 2-methoxyethanol or N,N-dimethylacetamide. The methods described above, as well as other known ones, suffer anyway from some drawbacks (use of expensive, toxic solvents, difficulty of purification, unsatisfactory yields) which restrict its industrial use.

More precisely, the purification step of crude diacerein is particularly critical.

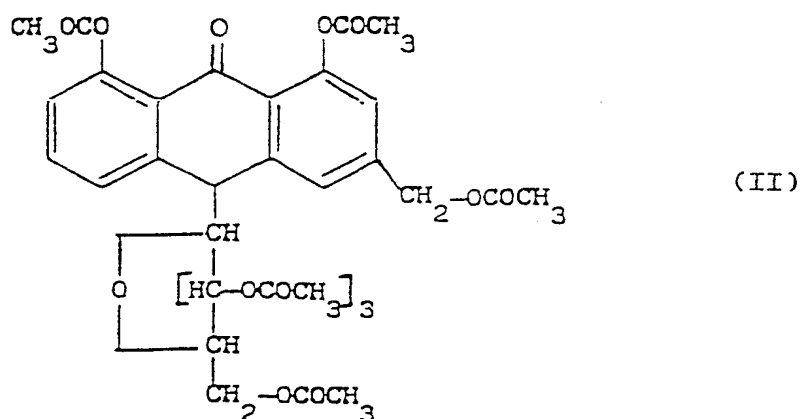
It has now been found a process for the preparation of diacerein which is advantageous compared with the known methods.

The process of the invention comprises:

a) acetylation of aloin, of formula (I):

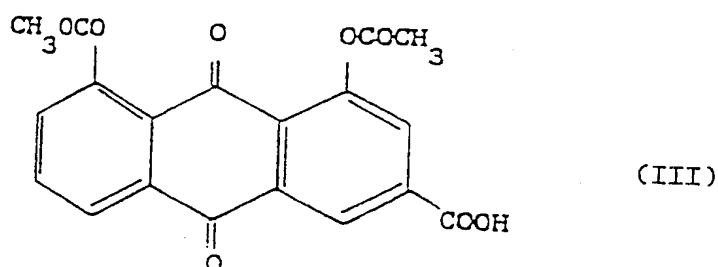


to give acetyl-barbaloin (II)



b) oxidation of acetyl-barbaloin (II) to give crude diacerein;

c) salification of the crude diacerein with an organic amine in aqueous or aqueous-acetonic solution, precipitation of the alkali salt by addition of an organic acid alkali salt and treatment with a diluted acid to give acid diacerein, of formula (III)



Step a) is preferably effected using acetic anhydride as acetylating agent.

The reaction is typically carried out using an acetic anhydride excess in the presence of bases such as
5 potassium acetate, at a temperature of about 130°-140°C.

Step b) is preferably carried out using chromic anhydride in acetic acid solution.

Chromic anhydride is used in excess to the stoichiometric, for example in molar ratios ranging from
10 5:1 to 10:1 compared with the starting aloin. The reaction temperature usually ranges from 40 to 60°C.

The oxidation is preferably carried out without previous recovery of the compound (II).

In step c), organic amines such as triethylamine, trimethylamine and the like can be used. Preferably,
15 triethylamine in acetone solution is used, which is added to an acetone aqueous solution of crude diacerein.

The organic acid alkali salt is preferably 2-sodium ethylhexanoate, added in acetone/isopropanol solution.
20 The sodium salt is filtered, washed with acetone and dried.

Any organic or inorganic acid, such as hydrochloric acid, sulfuric acid, acetic acid, p-toluenesulfonic acid, phosphoric acid, can be used for the conversion to
25 acid diacerein. Particularly preferred is the use of diluted phosphoric acid, at concentrations ranging from 1 to about 30%.

The following examples illustrate the invention in greater detail.

30 Example 1

A) A 1000 lt reactor is loaded with 25 kg of aloin,

8.8 kg of anhydrous potassium acetate and 125 kg of acetic anhydride. The mixture is heated to 135°C, keeping said temperature for 60 minutes, after that is cooled to about 50°C and added with 250 kg of acetic anhydride. Keeping the temperature at 55°C, a solution of 30 kg of chromic anhydride dissolved in 100 kg of acetic acid is added in about 4 hours. At the end of the addition, temperature is kept at 55°C for 30 minutes, then 210 kg of water are added. After cooling at 15°C, the reaction mixture is centrifuged and washed to neutrality with water, finally dried at 70°C. The yield in crude diacerein is 15 kg with a K.F. lower than 0.5%.

B) A 600 lt reactor is loaded with 15 kg of crude diacerein and 110 kg of acetone/water 90:10. The suspension is added with a solution of 5.3 kg of triethylamine in 65 kg of acetone to obtain the complete dissolution of the reaction mixture.

Separately, a solution of 9.7 kg of sodium 2-ethylhexanoate in 46 kg of an acetone-isopropanol 1:1 mixture is prepared. Diacerein sodium salt precipitates, which is centrifuged and dried at 70°C. The yield is 14.5 kg.

C) A 600 lt reactor is loaded with 15 kg of diacerein sodium salt and 300 kg of water to obtain a complete dissolution. Separately, a solution of 28 kg of 85% phosphoric acid and 160 kg of water is prepared, which is added to the reactor containing sodium diacerein in about 4 hours. A fine yellow crystal precipitates which is centrifuged, washed to neutrality with water and dried at 70°C. Yield

in pure diacerein 13 kg.

Example 2

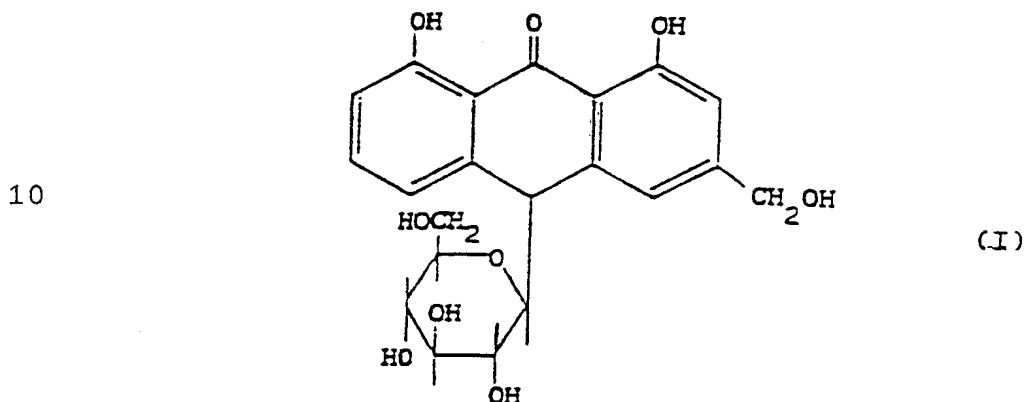
- 5 A) A 1000 lt reactor is loaded with 25 kg of aloin, 9 kg of anhydrous potassium acetate and 130 kg of acetic anhydride. The mixture is heated to 138°C keeping said temperature for 60 minutes, after that is cooled to about 50°C and added with 260 kg of acetic anhydride. Temperature is brought to 45°C, then a solution of 31 kg of chromic anhydride
10 dissolved in 105 l of acetic acid is added in about 5 hours, keeping said temperature. At the end of the addition, temperature is kept for 30 minutes, then 220 kg of water are added. After cooling at 15°C, the reaction mixture is centrifuged, washing
15 the cake with water to neutrality, then dried at 70°C. 15 kg of crude diacerein are obtained, having a 0.5% maximum K.F.
- 20 B) A 600 lt reactor is loaded with 15 kg of crude diacerein and 110 kg of acetone/water 90:10. The suspension is added with a solution of 5.2 kg of triethylamine in 60 kg of acetone to obtain the complete dissolution of the reaction mixture. Separately, a solution of 9.5 kg of sodium-2-ethylhexanoate in 45 kg of an acetone-isopropanol 1:1
25 mixture is prepared. Diacerein sodium salt precipitates, which is centrifuged and dried at 70°C. The yield is 14.3 kg.
- 30 C) A 600 lt reactor is loaded with 15 kg of diacerein sodium salt and 300 kg of water then, after dissolution, a solution of 29 kg of 85% phosphoric acid and 170 kg of water is added in about 4 hours.

The resulting yellow product is centrifuged, washed to neutrality with water and dried at 70°C. 12.9 kg of pure diacerein are obtained.

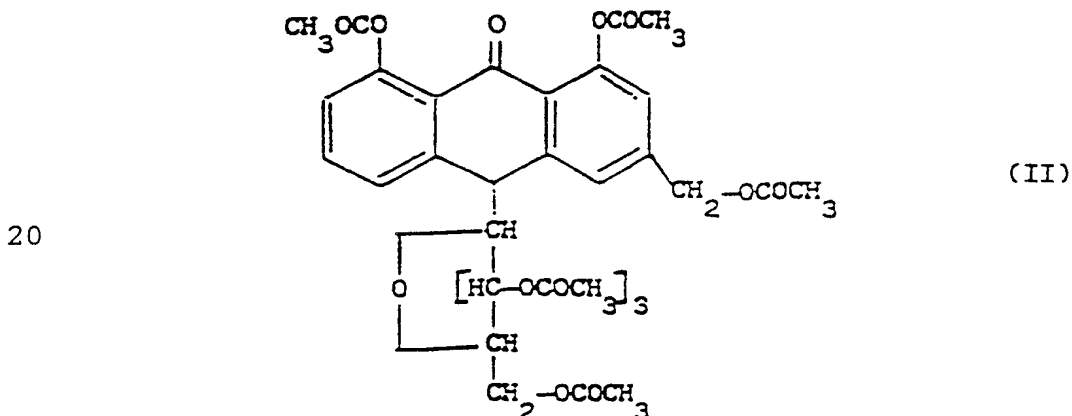
CLAIMS

1. A process for the preparation of diacerein, which comprises:

- 5 a) acetylation of aloin, of formula (I):



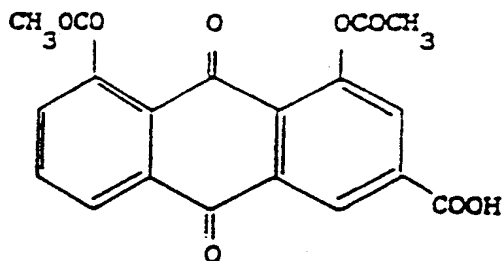
15 to give acetyl-barbaloin (II)



25 b) oxidation of acetyl-barbaloin (II) to give crude diacerein;

c) salification of the crude diacerein with an organic amine in aqueous or aqueous-acetonic solution, precipitation of the alkali salt by addition of an organic acid alkali salt and treatment with a diluted acid to give acid diacerein, of formula (III)

30



(III)

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2. A process as claimed in claim 1, wherein acetylation is carried out using an acetic anhydride excess in the presence of potassium acetate.
- 10 3. A process as claimed in claim 1 or 2, wherein step b) is effected using chromic anhydride in acetic acid solution.
4. A process according to any one of the above claims, wherein the crude diacerein is salified with
- 15 triethylamine.
5. A process according to any one of the above claims, wherein 2-sodium ethylhexanoate is used as organic acid alkali salt.
6. A process according to any one of the above claims,
- 20 wherein the precipitation of the salt takes place in a isopropanol-acetone 1:1 mixture.
7. A process according to any one of the above claims, wherein sodium diacerein is converted to acid diacerein by treatment with diluted aqueous phosphoric acid.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/03221

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C69/95 C07C67/40 C07C67/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 24572 A (STEBE BEHEER B.V.) 15 August 1996 see page 2, paragraph 1 see page 3, paragraph 3 - paragraph 4 see page 4, paragraph 2 - paragraph 6 see page 5 - page 7; examples 1-3 see page 8 - page 9; claims ---	1-5
X	EP 0 636 602 A (LABORATOIRE MEDIDOM S.A.) 1 February 1995 cited in the application see page 2, line 39 - page 4, line 7 see page 6; example 1 see page 8 - page 10; claims -----	1-3



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

6 October 1998

Date of mailing of the international search report

13/10/1998

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Information on patent family members

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EP 636602 A	01-02-1995	CA 2141247 A CZ 9500090 A HU 73498 A IT 1264545 B SK 4495 A US 5670695 A JP 7053462 A AT 165335 T DE 69409722 D DE 69409722 T ES 2115814 T	28-07-1996 17-07-1996 28-08-1996 02-10-1996 07-08-1996 23-09-1997 28-02-1995 15-05-1998 28-05-1998 13-08-1998 01-07-1998